invention commensurate in scope with the claims. Applicants respectfully traverse this rejection under 35 USC § 112, first paragraph.

As to claims 1 and 14 from which all rejected claims depend, there is no basis for the Examiner's opinion of lack of enablement, as is required to maintain such a rejection. Gould v. Mossinghoff, 229 U.S.P.Q. 1, 13-14 (D.D.C. 1985) aff'd in part, vacate in part, and remanded *sub nom*, Gould v. Quigg, 3 U.S.P.Q. 2d 1302 (Fed. Cir. 1987)("In examining a patent application, the P.T.O. is required to assume that the specification complies with the enablement provision of section 112 unless it has 'acceptable evidence or reasoning' to suggest otherwise"; the burden of persuasion is on the P.T.O.); In re Armbruster, 185 U.S.P.O. 152 (C.C.P.A. 1975).

The Examiner references neither the level of knowledge of "one of ordinary skill in the art," nor the nature of the impediments to enablement one might encounter. The Examiner is respectfully requested to provide an affidavit under §104(d)(2) as to the reasoning under which enablement is questioned.

In the alternative, Applicants respectfully request that this rejection be withdrawn.

The Examiner further rejected claims 1-10 and 14-22 under 35 USC § 112, first paragraph and stated that the specification , however, only discloses cursory conclusions without data supporting the finding, which state that the present invention provides a compound having a general formula, B-A-C can locally inhibit DP-IV activity. The Examiner further stated that the factors most relevant to this rejection are the breath of the claims, the presence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

Applicants traverse this rejection. In particular, Applicants refer to page 7, last line – page 8, lines 1-23. These passages clearly disclose that the goal of the invention is to **decrease or prevent a systemic** distribution of the DP IV-inhibitors of the present invention. The solution is given by means of voluminous hydrophilic substitutions on the side chain of DP IV-inhibitors, resulting in DP IV-inhibitors of the formula B-A-C. Preferred structures of these hydrophilic side chains are disclosed, e.g. at page 8, lines 16-23. Further, at page 8, lines 6-14, it is disclosed that the topical use encompasses the local use of the inhibitors by direct application to the tissue to be treated (e.g. skin, wounds, tumor). According to page 8, lines 11-14, topical use further

encompasses oral or anal administration of **non-absorbable or not readily absorbable** DP IV-inhibitors for the purpose of selectively influencing gastrointestinal DP IV. Example 1 and table 1 prove that the transportability of the side-chain-modified DP IV-inhibitors according to the present invention is dramatically diminished. The said DP IV-inhibitors are therefore excellently suited to achieving locally limited (topical) inhibition of DP IV in the body (page 9, last paragraph). With regard to enablement of the skilled person, the solution of the problem of the present application is provided in a clear way. Thus, applicants respectfully submit that the required enablement is provided and respectfully request this rejection be withdrawn.

Applicants respectfully submit that the claims remaining within the instant application are directed to various composition having the general formula B-A-C. The claims directed to a method of using these compounds as DPIV inhibitors have been withdrawn from consideration as a result of a restriction requirement.

In addition to the clear enablement of the claims remaining within the application, Applicants have provided multiple examples that contain specific criteria according to the invention of DP-IV inhibitors dosing within various animals studies the results of which can be extrapolated for use in humans by those skilled in the art without undue experimentation.

Applicants would respectfully direct Examiner's attention to the extensive specific criteria within Example 2 and Figure 1 that more than fully comply with the requirements of 35 USC 112, first paragraph. With specific reference to Example 2 and Figure 1, it is noted that no systemic action of orally administered side-chain-modified DP-IV inhibitors (exemplified in figure 1 are Glu(PEG)-Thia and Glu(Gly)5-Thia) in healthy Wistar rats is shown compared to the control compounds Glu-Thia and Ile-Thia, which are well absorbed from the intestine to the blood stream.

The utility of a chemical compound for a particular disease state may be confirmed by establishing that it possesses properties of therapeutic value through the aforementioned tests conducted on standard experimental animals. Applicants have disclosed examples and data on standardized laboratory animals, which can clearly be used by one skilled in the art to understand therapeutic utility. No undue experimentation is required to confirm the possession of such therapeutic effectiveness.

Applicants' situation is unlike that of Ex parte Stevens, 16 U.S.P.Q.2d 1379, 1380. In that case the applicant had **no** evidence whatsoever, either *in vivo* or *in vitro*, to support the alleged utility of treating cancer. Rather, in the present application there is ample evidence of treatment utility based upon the in vitro test results summarized in Example 1 and Table 1, and the animal test results summarized in Figure 1 and Example 2. The resulting data from standardized tests in vitro and upon experimental animals, provide a reasonable indication to one skilled in the art that the present invention would in fact have its asserted utility in Applicants' withdrawn claimed method for the use of these compounds as DP-IV inhibitors.

Applicants would point out that the Patent and Trademark Office has the burden of showing that the disclosure entails undue experimentation. In Re Angstadt (CCPA 1976) 537 F2d 498, 190 USPQ 214., It is respectfully submitted that the Patent Office has not carried this burden or provided the required reasonable basis for contending that one skilled in the art would not be able to practice the invention as claimed. Gould v. Mossinghoff 229 U.S.P.Q. 1, 13 (D.C. D.C. 1985) (emphasis added).

Applicants' claimed invention is more than fully supported by the instant specification. Accordingly, Applicants respectfully submit that any experimentation which might be required would not rise to the level of undue experimentation and therefore respectfully request that this rejection be withdrawn.

V. Claims 14-22 rejected under 35 U.S.C. 112, second paragraph.

The Examiner rejected claims 14-22 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants have amended claim 14 and respectfully submit that this rejection has been overcome.

VI. Rejection of Claims 14-17, 21 and 22 under 35 USC 102(b).

The Examiner rejected claims 14-17, 21 and 22 under 35 USC 102 (b) as being anticipated by Jenkins et al. (WO-95/15309)("Jenkins").

A. Examiner's Rejection: The Examiner stated that Jenkins discloses various dipeptidyl peptidase IV (DP-IV) inhibitors such as Glu(NH(CH2)5COOBn)phyrrolidide (compound 59 in

Table 2) and Glu(NH(CH2)5COOBn) cyanopyrrolidide (Compound 97 in Table 2), where the side chain of Glu is covalently linked to a NH(CH2)5COOBn, which is a substituted amine having 12 carbon atoms; and the inhibitors were tested in Hepes pH 7.8 buffer solution for their inhibition against DP-IV (pages 9-10; Table 9; claims 14-17,21 and 22).

B. Amendments to the Claims: Applicants respectfully suggest that the claim 14 as amended from which all other rejected claims depend is no longer anticipated by Jenkins and subsequently neither are its dependent claims. Applicants respectfully request that the rejection be withdrawn.

III. Rejection of Claims 14-17, 21 and 22 rejected under 35 USC 102(b).

The Examiner rejected claims 14-17, 21 and 22 under 35 USC 102 (b) as being anticipated by Ashworth et al. (Bioorg. Med. Chem. Lett. 6, 1163-1166 (1996)) ("Ashworth").

A. Examiner's Rejection: The Examiner stated that Ashworth discloses a series of DP-IV inhibitors such as Lys(Z)-cyanopyrrolidide (compound 28 in Table II), where the side chain of Lys is covalently linked to Z group (C6H5CH2OCO-), which is a substituted aromatic compound having 8 carbon atoms. The Examiner further state that the inhibitors were tested in pH 7.4 buffer solution for their inhibition against DP-IV (Table II, page 1166; claims 14-17, 21 and 22).

B. Amendments to the Claims: Applicants respectfully suggest that claim 14, as amended and from which the other rejected claims depend, is no longer anticipated by Ashworth and subsequently neither are its dependent claims. Accordingly, Applicants respectfully request that the rejection be withdrawn.

VIII Rejection of Claims 1-4, 7, 9, 10, 14-17, 20 and 22 rejected under 35 USC 102(e).

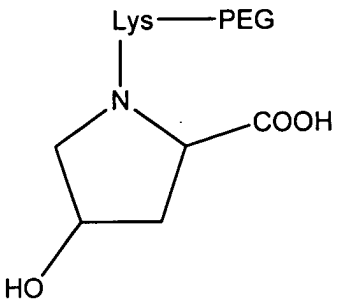
The Examiner rejected claims 1-4, 7, 9, 10, 14-17, 20 and 22 under 35 USC 102 (e) as being anticipated by Kohn et al. U.S. Patent No. 6,517,824 ("Kohn").

A. Examiner's Rejection: The Examiner stated that Kohn discloses an antifibrotic composition comprising a copolymer conjugate of L-proline derivative such as poly(PEG-Lys) 4-hydroxyproline (scheme 4b, compound 17; Example 13; claims 1-4), where the side chain amine is covalently linked to PEG having a molecular weight from about 500 to about 15,00 (column 4, lines 59-63; claims 7 and 20), and a pharmaceutically acceptable carrier including diluents,

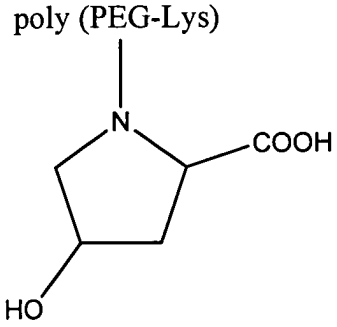
solubilizer, enhancers and buffers (column 5, lines 46-64; column 8, lines 9-21; claims 9, 10, 14-17 and 22).

B. Teachings of Cited Reference:

A compound of the present claimed invention has the formula A (see below). The compounds of the present invention (formula A) are different from the compounds disclosed in Kohn (formula B).



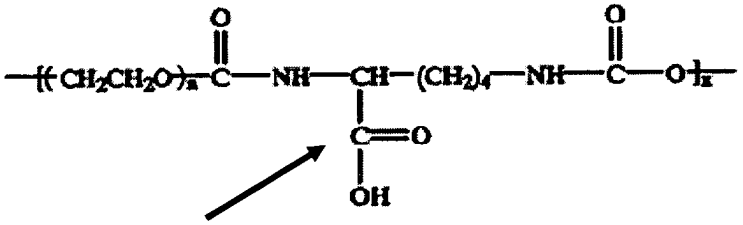
A



B

The compounds in Kohn consist of a polymer of PEG-Lys [poly(PEG-Lys)], which is represented by Formula (III) in column 14 of Kohn.

(III)



The Kohn compounds comprise **x** molecules of PEG-Lys. The hydroxyproline residue is coupled to the carboxy group as indicated by the arrow above. Because of that, the number of hydroxyproline residues bound to poly(PEG-Lys) is dependent from **x,** but is in any event more than one, because it is defined as a polymer.

The compounds of the claimed invention, when compared directly with the specific compounds disclosed in Kohn, would comprise exactly **one** PEG-Lys molecule, which would be bound to **one** hydroxyproline residue. Consequently, Kohn does not disclose compounds of Applicants' claimed invention. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

The claims remaining within the application are believed to patentably distinguish over the prior art and to now be in condition for allowance. Early and favorable consideration of this application is respectfully requested.

Respectfully submitted,

John C. Serio, Reg. No. 39,023
Attorney for Applicants
Customer No. 21710
Brown Rudnick Berlack Israels LLP
One Financial Center, Box IP
Boston, MA 02111
Tel: (617) 856-8238
Fax: 617-856-8201
Email: ip@brbilaw.com

Dated: May 19, 2004